DISSERTATION ON

RISK FACTORS FOR SEIZURES IN CHILDREN WITH CEREBRAL PALSY

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CERTIFICATE

This is to certify that this dissertation titled **"Risk factors for Seizures in Children with Cerebral Palsy** - Case control Study" is a bonafide work done by **Dr.B.Rajesh Kannan** Post Graduate Student, Institute of Child Health and Hospital for Children under Madras Medical College, Chennai, during the Academic years 2007 - 2010.

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CONTENTS

SL.NO.	TITLE	PAGE NO.
1.	INTRODUCTION	1
2.	HISTORY	2
3.	CEREBRAL PALSY	3
4.	REVIEW OF LITERATURE	12
5.	AIM OF THE STUDY	23
6.	MATERIALS & METHODS	24
7.	RESULTS	32
8.	DISCUSSION	43
9.	CONCLUSION	52
10.	BIBLIOGRAPHY	54

INTRODUCTION

Cerebral Palsy is the most common neurological disability seen in children. The estimated prevalence of cerebral palsy in the developed countries is 2/1000 population. The prevalence in a developing country like ours, is much higher, figures quoted being as high as 20 per 1000 live births. Epilepsy has been estimated to occur in 10-40% of cases, but its likelihood depends on the type of cerebral palsy.

With a large population, the magnitude of the problem is enormous in India. This is a drain on the national economy, not only by means of the medical and other expenditure on these unfortunate children, but also in the form of loss of valuable human resources, which these youngsters would otherwise have contributed to the development of our nation. Emotional sufferings and lost opportunities add immeasurably to the burden of the affected families. Hence, it is upon us to probe into the cause of this malady and to go all out to offer protection of our children from this developmental disaster and its complications.

It is 150 years since Little's attribution of Cerebral Palsy to difficult deliveries and a century since Freud challenged it on the grounds of an underlying developmental disorder being the basic cause. The question is unanswered till date and the exact role of particular factors still debatable.

Knowledge of the etiology is important not only to protect the children from cerebral palsy but also from seizures as it is also significant in the light of present day consumerism and its medico-legal implications.

HISTORY

In 1827, Cazauvielh, a French physician, first studied Cerebral Palsy scientifically correlating it with the brain functions. It was left to Little for a detailed and documented study and he attributed it to birth trauma and asphyxia neonatorum in the year 1862. The eponymous Little's disease evolved from his extensive work. Freud countered this in 1897 and emphasized on intrauterine developmental abnormality and less on birth trauma. Gennie Colby started physiotherapy for Cerebral Palsy, while Elizabeth Lord added the new dimension of mental health. Stoffel described surgical correction of spastic contracture while Phelps established a comprehensive community rehabilitation center in Maryland. The National Society for Crippled Children and Adults established a separate Cerebral Palsy division and in 1947, the American Academy for Cerebral Palsy (AACP) was born in Chicago. Technological improvements in perinatal care from 1960 to the present have taken strides and Mertatz and Johnson emphasized the role of improved perinatal care in the prevention of this malady.

CEREBRAL PALSY

DEFINITION

Cerebral Palsy is a static encephalopathy that may be defined as a non-progressive disorder of posture and movement, often associated with epilepsy and abnormalities of speech, vision and intellect resulting from a defect or lesion of the developing brain (1).

PREVALENCE

Cerebral Palsy is a common disorder with an estimated prevalence of 2/1000 population in developed countries. The prevalence is much higher in developing countries, estimates showing as high as 20 per 1000 live births (2). Epilepsy 10-40% but its likelihood depends on the type of Cerebral Palsy (5)

ETIOLOGY

One hundred and fifty years ago, Little considered birth asphyxia and trauma as well as prematurity as the primary causes (3) and it was held on to until recently. There is a change in trend in the present thinking, after this large study like the National Collaborative Perinatal Project (NCPP) (1)

CLASSIFICATION

Cerebral Palsy may be classified by a description of the motor handicap in terms of physiologic, topographic and etiologic categories and functional capacity (6).

TABLE - I

Physiologic	Topographic	Etiologic	Funtional
Spastic	Monoplegia	Prenatal	Class I - no limitation of activity
Athetotic	Paraplegia	Perinatal	
Rigid	Hemiplegia	Postnatal	Class II - slight to moderate limitation
Ataxia	Triplegia		
Tremor	Quadriplegia		Class III - moderate to great limitation
Atonic	Diplegia		
Mixed	Double hemiplegia		Class IV - no useful activity
Unclassified			

The physiologic classification identifies the major motor abnormality, whereas the topographic taxonomy indicates the involved extremities.

PATHOLOGY

TABLE - II

	Type	Site of Lesion	Sequel
I	Selective neuronal necrosis	Cerebral cortex brainstem cranial nerve nuclei	Spastic Quadriplegia
II	Status marmaratus	Basal gangalia	Athetoid CP
III	Para sagittal cerebral injury	Cerebral cortex (superomedial convexity)	Quadriplegia Paraplegia
IV	Periventricular leucomalacia	White fibres innervating the leg through the internal capsule	Spastic Diplegia
V	Focal and multifocal encephalomalacia	Porencephaly	Any type of CP.

SEIZURES

DEFINITION - Recurrent excessive and/or hypersynchronous electrical discharges of neurons, which, for practical purposes, are located within the cerebral cortex.

Basic mechanisms : (5)

- abnormalities at the cell membrane level (ion channels & receptors) and in Neuronal Circuits
- Voltage-gated ion channels determine the excitability of neurons as well as participating neurotransmission

Three main classes of Voltage - gated ion channels have been described Na^+, Ca^{2+},K^+.

- Na^+ currents are involved in the generation of action potentials
- K^+ current cause hyperpolarization and hence stabilize the neuronal membranes.
- Both Na^+ & Ca^{2+} currents are involved in the generation of burst discharges.
- Ligand - gated ion channels are activated by the binding of a neurotransmitter to the ion channels receptor.
- Gamma - aminobutyric acid and glycine are inhibitory neurotransmitters glutamate & asparatate are excitatory neurotransmitters

CLASSIFICATION OF SEIZURES (1)

International classification of epileptic seizures

❖ **Partial Seizures**

- Simple Partial (consciousness retained)

  Motor

  Sensory

  autonomic

  psychic

- **Complex Partial (consciousness impaired)**

  Simple partial, followed by impaired consciousness

  consciousness impaired at onset

- **Partial Seizures with Secondary Generalization**

❖ **Generalized Seizures**

- Absence

  Typical

  Atypical

- **Generalized tonic - clonic**

  Tonic

  Clonic

  Myoclonic

  Atonic

  Infantile Spasms

- **Unclassified Seizures**

CLINICAL MANIFESTATIONS

Spastic Hemiplegia

Decreased spontaneous movements on the affected side.

Hand preference at an early age.

Arm is more involved than the leg.

Spasticity in the affected extremities.

Brisk deep tendon reflexes.

Ankle clonus and Babinski sign.

One third have seizures that usually develops during the 1 year or 2 and 25% have mental retardation.

CT Scan

Atrophic cerebral hemisphere with dilated lateral ventricle on the contralateral side.

Spastic Diplegia

Dragging of legs as the infant crawls.

Legs more affected than the arms.

Bilateral spasticity of the legs.

Brisk reflexes, ankle clonus and bilateral Babinski sign.

Normal intellectual development in most of the cases;

Seizures also minimal.

CT Scan

Periventricular leukomalacia

Spastic Quadriplegia

Most severe form of Cerebral Palsy.

Marked motor impairment of all extremities.

Supra nuclear bulbar palsy.

Spasticity, brisk reflexes and Babinski sign.

Associated developmental disabilities including mental retardation, seizures, even 90%

Visual and speech abnormalities particularly prevalent.

Lesions in cerebral cortex, brainstem and cranial nerve nuclei.

Athetotic Cerebral Palsy

Relatively rare with the advent of aggressive management of neonatal

hyperbilirubinemia and prevention of kernicterus.

Hypotonia - marked head lag.

Athetoid movements by one year of age.

Feeding and speech difficulties common.

Seizures uncommon, intellect preserved in most.

DIAGNOSIS

Thorough history and physical examination are essential to exclude a progressive disorder of the central nervous system, including degenerative diseases, spinalcord tumour or muscular dystrophy. Depending on the severity and nature of neurologic abnormalities, a baseline EEG and Neuro imaging may be done to determine the location and extent of structural lesions or associated congenital malformation. Additional studies include tests of hearing and visual function.

Electro encephalogram

- Is the single most useful investigation is children with Seizure disorder.

Uses of EEG is clinical practice

- help to establish the likely diagnosis of epilepsy
- help to establish the likely type of epilepsy
- help to establish the likely possible precipitating factors
- to investigates the cause of cognitive decline
- help to localize the onset of focal seizure
- to monitor treatment including the timing of drug withdrawal.

TREATMENT

Early intervention therapy which stresses on early identification and management to prevent complications and promote development is necessary. Multidisciplinary approach with a team of physicians from various specialties as well as occupational and physical therapists, speech pathologist, social worker, educator and developmental psychologist forms the crux of the management.

Parent education as to handling the baby, exercises to prevent contracture, drugs to reduce seizures and spasticity, adaptive equipments like walkers, frames and calipers, surgical soft tissue procedures and posterior rhizotomy to reduce muscle spasm are important aspects of

management. Occupational therapy including motorized wheel chair, special feeding devices, modified typewriters, etc. are additional aspects. Control of seizures and management of other associated handicaps are part of the treatment.

REVIEW OF LITERATURE

William Little, while writing in the transactions of the Obstetric Society of London, in 1862, "on the influence of abnormal parturition, difficult labour, premature birth and asphyxia neonatorum on the mental and physical conditions of the child, especially in relation to deformities" (3) was certain that the origins of Cerebral Palsy were related to the birthing process and he succeeded in establishing that belief which remained unchanged until a decade ago. However, this was countered by Sigmund Freud in as early as 1897, when he stated that "since the abnormal process of birth frequently produces no effect, one cannot exclude the possibility that, despite Little's anamnesis, diplegia still might be of congenital origin. Difficult birth in itself in certain cases is merely a symptom of deeper effects that influenced the development of the fetus" (7). And the feud goes on, after a century.

The Problem and its magnitude

The prevalence of Cerebral Palsy among children at school entry is about 2 per 1000 live births in developed countries (8.9). It is much higher in developing countries, however.

The Metropolitan Atlanta Developmental Disabilities study was conducted by Marshalyn Yeagrin et al (10). This is a population based multisource method study to assess the prevalence of developmental disabilities in children. The study population consisted of children who were 10 years of age between 1985 and 1987. The prevalence rate of Cerebral Palsy found in this study was 2 per 1000 ten year old children.

Swedish studies (11, 12, 13, 14, 14a) analysed the epidemiological trends in cerebral

palsy over a 20 year period based on a population based series of Cerebral Palsy patients born in 1959 - 1978, and again in the four year period 1979 - 1982. After a significantly decreasing incidence of Cerebral Palsy from 1959 to 1970 from 1.9 to 1.4 per 1000 live births, there was a significant increase reaching 2.0 per 1000 from 1970 to 1978. In 1979 - 1982, it was 2.17/1000, 1.33 for children born at term and 0.94 for preterms. Both the decreasing trend in earlier periods and the increasing trend that occurred later were mainly referable to spastic / ataxic diplegia in preterm Cerebral Palsy and to dyskinetic syndromes in Cerebral Palsy infants born at term. With respect to pathogenesis, the corresponding changes in Cerebral Palsy incidence were mainly accounted for by the group with potential perinatal risk factors. Analysed on the basis of birth weight specific groups, the incidence of Cerebral Palsy increased in all groups, but to a statistical significant extent for birth weights below 1500 g and over 2500 g. The rising prevalence of Cerebral Palsy was concomitant with a parallel fall in perinatal mortality, especially in very preterm infants.

The prevalence trend of Cerebral Palsy in the United Kingdom is well brought out by the two national cohort studies namely the British Perinatal Mortality Survey of 1958 and the British Births Survey of 1970 (15). The prevalence remained constant at 2.5/1000 births over the 12 year period. During this 12 year period, there were reductions in the rate of still births and in neonatal mortality.

Another study from England by Pharaoh and colleagues confirms the above fact (16). This study found no discernable trend on the overall prevalence of Cerebral Palsy from 1967 to 1984, the prevalence ranging from 1.18 to 1.97 per 1000 live births in the Mersey region, where the study was conducted. But there was a significant upward trend in the prevalence of

all the major types of Cerebral Palsy among the low birth weight infants.

Jarvis et al (17) conducted a study in North East England and analysed the trend of prevalence of Cerebral Palsy between 1960 and 1975. The overall congenital Cerebral Palsy rate showed a gradual rise (mean 1.64 per 1000 live births). There was a fall in the rate of Cerebral Palsy among very low birth weight (VLBW) babies. The rate, however, rose among babies weighing more the 2.5 kg at birth. This is in variance with the previous two studies from England.

The series from Western Australia (18) covering the period 1967 - 1985 showed an increase in cerebral palsy especially in infants under 1500 g from 12.1 in 1968 to 64.9 in 1985.

This being the state of affairs among the various developed countries, we shall now look into the Indian statistics (2). The magnitude of problem in India is much higher and is widely quoted as 20 per 1000 live births., i.e., as much as 10 times higher than the average of 2 per 1000 among the developed countries as seen above.

Kulak W, Sobaniec W.(67) from Poland evaluated the risk factors, incidence and prognosis of epilepsy in Cerebral Palsy. Though epilepsy occurs in 15-90% of children with Cerebral Palsy (CP). 198 children with CP were included in the study between 1994 and 2001. Low birth weight, neonatal seizures, seizures during the first year of life, family history of epilepsy, severity of CP and Computer Tomography findings were found to be related to significantly increased risk of epilepsy in children with CP in the logistic regression analysis. The overall epilepsy incidence was 41.4%. Epilepsy most commonly affected children with spastic tetraplegia 65.6%. Intractable epilepsy occurred in 51.2%, while in spastic tetraplegia it was even higher (60%). Controlled epilepsy was observed in 83.3% of spastic diplegia and in 72.7% of spastic hemiplegia. Polytherapy was commonly used in children with spastic tetraplegia 59.5%. Partial seizures with secondary generalization, infantile spasms and Lennox-Gastaut syndrome were the most frequently observed seizures in epileptic children with CP. Epilepsy is common in children with CP and has poor prognosis.

Pratibha Singhi, MBBS, MD Sujeet Jagirdar, MBBS, MD Narendra Khandelwal, MBBS, MD Prahbhjot Malhi, MA, PhD (73) from Chandigarh studied the spectrum of epilepsy in children with cerebral palsy, 105 consecutive children with cerebral palsy and active epilepsy, between 1 and 14 years of age, were studied prospectively. Of the 105 children, 65 were male, 40 of 105 (38%) had a history of birth asphyxia. The mean age of onset of seizures was 18.9 months; 64 (60.95%) had seizure onset before 1 year of age. Children with myoclonic seizures ($P < .05$) and infantile spasms ($P < .01$) had seizure onset significantly early in life. Generalized seizures were the most common, followed by partial seizures, infantile spasms, and other myoclonic seizures. Seizures were controlled in 45 (58.1%) children, and polytherapy was

required in 40 children. EEG and CT abnormalities were seen in 70.5% and 61% of the children. Seizure control was achieved in 74% of the patients with a normal to borderline social quotient compared with 48.7% with a social quotient less than 70. Social quotient values had a positive correlation with age of onset of seizures ($P < .01$) and with better control of seizures ($P < .01$). A retrospective cohort of 452 cases of cerebral palsy was studied to find the prevalence of epilepsy in cerebral palsy. A control group of 60 age-matched children with cerebral palsy but no epilepsy was also studied for comparison of the social quotient. Of the cohort of 452 children, 160 (35.4%) had epilepsy. The maximum incidence (66%) was seen in children with spastic hemiplegia, followed by quadriplegia (42.6%) and diplegia (15.8%). Epilepsy in cerebral palsy is seen in about one third of cases; it is often severe and difficult to control, particularly in children with mental retardation.

Kwong KL,Wong SN,So KT(46) et al conducted this retrospective study which reviewed the prevalence, nature, and prognosis of epilepsy in cerebral palsy. Epilepsy occurs in 15-60% of children with cerebral palsy. However, its clinical course is not well defined. Thirty-two of 85 children with cerebral palsy had epilepsy. A control group of 59 epileptic children with normal neurodevelopment status was seen during the same period. Epilepsy most commonly affected patients with spastic tetraplegia and those with mental subnormality. When compared with controls, children with cerebral palsy had a higher incidence of epilepsy with onset within the first year of age (47% vs 10%), history of neonatal seizures (19% vs 3%), status epilepticus (16% vs 1.7%), polytherapy (25% vs 3%), and treatment with second-line antiepileptic drugs (31% vs 6.7%). They had a lower incidence of generalized seizures (25% vs 59%) and remaining seizure free (37% vs 90%). Factors associated with a seizure-free

period of 1 year or more in epileptic children with cerebral palsy were normal intelligence, single seizure type, monotherapy, and spastic diplegia. Epilepsy was common in children with cerebral palsy. Further larger studies are required to delineate other prognostic factors.

A K Gururaj,L.Sztriha,A Bener,A.Dawodu and V.Eapen(55) from United Arab Emirates (1997-1999) studied the occurrence, associated factors, nature and prognosis of seizures in children with cerebral palsy. A prospective, descriptive, hospital based case-control study. Fifty-Six children with CP and seizures. Control groups of 35 children with CP without seizures. Spastic tetraplegia was the commonest type of CP associated with seizures whereas spspastic diplegia was the commonest variety of CP in control group. Most children with CP had an early onset of seizures within the first year of life as against those without CP. The children in group 1 had a higher incidence of neonatal seizures (42.9% vs. 29.4% in group 2 and 0% in group 3), presence of significant developmental delay (98.2% vs. 20.0% in group 3), occurrence of significant abnormalities on brain imaging (94.6% vs. 196% in group 3) and a need for use of more than 1 antiepileptic drug (66.1% vs. 30.0% in group 3). Over half of children in the study group presented with generalized tonic clonic seizures; the electroencephalogram (EEG) showed focal epileptic discharges with or without secondary generalization in 39.3%. The overall outcome of seizures in children with CP was poor needing prolonged course of anticonvulsant medications, polytherapy and higher incidence of refractory seizures and admissions for status epilepticus compared to the control group. Cerebral Palsy is associated with a higher incidence of seizure disorders, which, in a majority, has its onset in the neonatal period. Brain imaging showed abnormal pathology in most affected children, which possibly accounts for the tendency to more refractory seizures in these

children.

Sugiura C, Shiota M, Ieshima A, Ohno K.(68) Japanese 2003 Nov; This study was designed to investigate the incidence and prognosis of epilepsy in 109 patients with cerebral palsy and to attempt to correlate these clinical data with the type of palsy. The incidence of epilepsy, the onset of age and the type of first seizure were associated with the regions affected by palsy. A good association exists between tetraplegia and age-dependent epileptic encephalopathy. In patients with cerebral cortical lesions demonstrated by radiological examination, the incidence of epilepsy was significantly increased. The prognosis of epilepsy is not related to the type of palsy. In spastic palsy, the patients with epilepsy showed more severe intellectual disabilities.

Bruck I, Antoniuk SA, Spessatto A, Bem RS, Hausberger R, Pacheco CG.(69) Parana 2001 Mar; to describe the prevalence and characteristics of epilepsy in patients with cerebral palsy.100 consecutive patients with Cerebral Palsy were retrospectively studied. Types and incidence of epilepsy were correlated with the different forms of cerebral palsy. Other factors associated with epilepsy such as age of first seizure, neonatal seizures and family history of epilepsy were also analyzed. The overall prevalence of epilepsy was 62%. Incidence of epilepsy was predominant in patients with hemiplegic and tetraplegic palsies: 70.6% and 66.1%, respectively. First seizure occurred during the first year of life in 74.2% of patients with epilepsy. Generalized and partial were the predominant types of epilepsy (61.3% and 27.4%, respectively). Thirty-three (53.2%) of 62 patients were seizure free for at least 1 year. Neonatal seizures and family history of epilepsy were associated with a higher incidence of epilepsy. Epilepsy in Cerebral Palsy can be predicted if seizures occur in the first year of life, in neonatal

period and if there is family history of epilepsy.

Zelnik N, Konopnicki M, Bennett-Back O, Castel-Deutsch T, Tirosh E. (70) Israel 2009 July; The purpose of the study was to identify predictive risk factors for epilepsy among children with cerebral palsy. We conducted a retrospective study of the clinical characteristics of children with Cerebral Palsy and epilepsy in comparison to those of children with Cerebral Palsy without epilepsy. The examined parameters included: the prevalence and the age of onset of the seizures, the clinical subgroup of cerebral palsy and subtype of epileptic seizures. We looked for possible risk factors including the presence of neonatal seizures, the imaging findings, the gestational age at delivery, the adjusted birth weight, the mode of delivery, the Apgar scores, and the head size as well as the presence of consanguinity. Epilepsy occurred in 33% of the studied children. Almost 50% of the epileptic children had their first seizure within the first 12 months of life. Neonatal seizures were strong predictors for epilepsy ($p<0.001$). Presence of at least one abnormal structural finding (particularly brain atrophy) was also a significant predictor of epilepsy ($p<0.003$). Low Apgar score at 5min after birth and birth at term were also found more frequently among patients with epilepsy, although when adjusted with other risk factors, Apgar score did not reach statistical significance. The mode of delivery, head circumference, adjusted birth weight, gender and ethnic group, consanguineous marriage and prematurely were not found to be risk factors for the occurrence of epilepsy in these children.

Hadjipanayis A, Hadjichristodoulou C, Youroukos S.(71) Greece,1997 Oct; The incidence of epilepsy in 323 patients with Cerebral Palsy (CP) was 41.8%.Almost half of the patients with spastic tetraplegia and hemiplegia had epilepsy. The incidence was lower in

patients with spastic diplegia. No sex differences were observed. Partial seizures were by far the most common form of epilepsy in spastic hemiplegia, while generalized tonic-clonic episodes predominated in all other forms of CP. A very high incidence of West syndrome was observed in patients with spastic tetraplegia. Most of the patients with spastic tetraplegia had their first seizure in the first year of life. In patients with spastic hemiplegia the onset of epilepsy was often delayed for several years. A high rate of polytherapy was recorded, but two-thirds of the patients remained seizure-free for long periods. In just over one-fifth of the patients successful withdrawal of medication was achieved.

AIM OF THE STUDY

To find out the risk factors for Seizures in children with Cerebral Palsy.

MATERIALS AND METHODS

1. Methodology

Study Design : Case Control Study

Study Place : Department of Paediatric Neurology

ICH & HC.

Study Period : Sep 07 - Aug 09

2. Study Specifications

Case : Cerebral Palsy with Seizures

Control : Cerebral Palsy without Seizures

Inclusion Criteria :

Cerebral Palsy children aged 1-12 yrs.

Exclusion Criteria :

Suspected case of Neurodegenerative disorder

Family history of similar illness.

3. Sample Size

All children with Cerebral Palsy attending the out patient department during the study period will be included.

4. Description of Manoeuvre

All children with CP attending our pediatric Neurology op will be registered.

Demographic details, history, clinical details and anthropometry will be recorded in a pre structured proforma. The proforma will be used to collect the data from the history obtained from mother and from medical records whenever available.

Frequency of risk factor will be measured in both groups (Case and Control)

Mother of case and control will be involved in a similar manner.

5. Outcome measurement

The outcome measured was association of various risk factor for seizure in children with CP

The group of risk factors for seizures with cerebral palsy considered were

A. Demographic profile and family history

B. Maternal factors

C. Foetal factors

D. Labour and delivery related factors

E. Postnatal factors

The demographic factors and family history which were considered as a risk factor along with rural and urban area. In rural areas where there is no easy availability of medical facilities. Maternal literary rate, maternal illiteracy was defined as mother not having attended school and / or cannot read or write. Presence of family history of neurological illness with seizures/ acquired neurological illness or neurodegenerative disorders were enquired in the immediate family members namely mother, father, siblings, uncle, aunts and first cousins.

Maternal factors considered were place of delivery home or institutional. Type of delivery Normal vaginal, prolonged vaginal, LSCS, Forceps, Breech and Vacuum. Prolonged vaginal was define as duration of second stage of labour >1 hour both in primigravida and multigravida. The second stage of labour is defined as internal between the rupture of membrane to delivery of the child. History of birth asphyxia if the record present (as noted by Apgar) or there is delayed crying needed resuscitation. History of multiple births.

Foetal factors

Maturity, birth weight, neonatal seizures and H/O Neonatal Jaundice. Preterm was defined as gestational age < 37 weeks based on mother's history or documents available. Term is completed 37 weeks of gestation. Post term GA > 42 weeks.Low birth weight was defined as birth weight <2500gm

History of Neonatal seizures from birth to 28 days of life. And history of Neonatal jaundice all these dates are collected from mother's history or documents available. Postnatal factor considered is h/o Seizures during the first year of life.

Statistical Analysis

Prevalence of risk factors will be estimated in both the case and control to calculate odds ratio.

PROFORMA

Reg.No. :
Date :

1.	Name	-	
2.	Sex	1.	Male
		2.	Female
3.	Age (in months)		
4.	Address	1.	Rural
		2.	Urban
5.	Socio – Economic status	1.	Daily wages
		2.	Salaried
		3.	Gazetted Officer
		4.	Business
6.	Maternal Education	1.	Illiterate
		2.	Primary
		3.	Middle School & Above
		4.	College
7.	Father's Education	1.	Illiterate
		2.	Primary
		3.	Middle School & Above
		4.	College

Maternal

8.	Place of delivery	1.	Home
		2.	Hospital
9.	Type of delivery	1.	Normal Vaginal
		2.	Prolonged Vaginal
		3.	LSCS
		4.	Forceps
		5.	Breech
		6.	Vacuum

10.	H/o Birth asphyxia as per history	1. Present 2. Absent

Neonatal

12.	Maturity	1. Preterm - As per History 2. Preterm - As per History + Record 3. Term - As per History 4. Post term - As per History + Record 5. Post term - As per History 6. Post term - As per History + Record
13.	Birth Weight	1. Low Birth Wt as per History 2. Low Birth Wt as per History +Record 3. Normal Birth Wt History 4. Normal Birth Wt History + Record
14.	H/o Neonatal Seizures	1. Present 2. Absent
15.	H/o Hyperbilirubinemia	1. Present As per History 2. Present As per History + Record 3. Absent As per History 4. Absent As per History + Record
16.	H/o Seizures during the 1st year of life	1. Present 2. Absent
17.	Family H/O Seizures	1. Present 2. Absent
18.	Type of CP	1. Spastic Hemiplegia 2. Spastic Diplegia 3. Spastic quadriplegia 4. Dyskinetic 5. Mixed 6. Hypotonic

19. Severity of CP (Functional classification)

1. Able to carryout activity of daily living
2. Ambulant with out support
3. Ambulant with support
4. Bed ridden

20. Type of Seizure

1. GTCS
2. GTS
3.Myoclonic
4.Absence
5. Focal Motor
6. CPS
7. Status Epilepticus
8. Febrile Seizure
9. Others

21. Pattern of Seizure

1. Single Type
2. Multiple Types

22. Maximum Duration of Seizure during the past

1. > 5mins
2. 5-30
3.>30 mins

23. No. of fits on an average of one year

1. Single Episode
2. 2-6 Episodes
3. >6 Episodes

24.	On Medication	1. Monotherapy 2. Polytherapy 3. Not taking treatment
25.	CT Findings	1. Cong. Malformations 2. Intracranial Haemorrhage 3. Periventricular Leucomalacia 4. Other
26.	EEG findings	1. Normal 2. Abnormal

RESULTS

Two hundred cases of Cerebral Palsy with Seizure and 200 controls were included in the study. Children aged 1-12 yrs were included cases and controls were block matched for sex.

TABLE - III

DISTRIBUTION BY SEX

Sex	Case (n = 200)	Control (n = 200)
Male	71.6% (143)	55% (111)
Female	28.4% (57)	45% (91)

Male preponderance was noticed is cases and controls. (Table - 3)

TABLE - IV

DISTRIBUTION BY ADDRESS

	Case (n = 200)	Control (n = 200)
Rural	56.3% (112)	69.8% (141)
Urban	43.7 (88)	30.2% (59)

Both rural and urban population are affected with slight increase towards rural population.

TABLE - V

DUSTRIBUTION BY SOCIO ECONOMIC STATUS

Socio Economic Status	Cases (n = 200)	Control (n = 200)
Daily wages	52.8% (104)	44.1% (89)
Salary	28.9% (58)	21.3% (42)
Gazetted Officer	11.2% (23)	5.4% (12)
Business	7.1% (15)	28.7% (57)

Low Socio economic status group affected more.

TABLE - VI

DISTRIBUTION BY EDUCATION

	Maternal		Father	
	Case	Control	Case	Control
Illiterate	21.8 (48)	21.8 (44)	20.3 (40)	32.7 (64)
Primary	22.3 (56)	22.3% (45)	28.4 (56)	22.8 (46)
Middle School & Above	30.7 (74)	30.7% (60)	32.5 (64)	22.3 (45)
College	25.2 (22)	25.2 (51)	18.8 (40)	22.3 (45)

No Significance between the parental education and Cerebral Palsy.

TABLE - VII

PLACE OF DELIVERY

	Cases (n = 100)	Control (n = 100)
Home	7.1% (14)	14.9% (30)
Hospital	92.9% (186)	85% (170)

In case group home delivery contributed to 7%

TABLE - VIII

DISTRIBUTION BY TYPE OF DELIVERY

Type of Delivery	Case (n = 200)	Control (n = 200)
Normal Vaginal	51.3% (104)	40.8% (115)
Prolonged Vaginal	23.4 (46)	20% (20)
LSCS	17.3% (34)	30.2% (59)
Forceps	6.6 (13)	3% (6)
Breech	1.5 (3)	-
Vacuum	-	-

Normal Vaginal Delivery is more in case and control group. Prolonged Vaginal Delivery is equal in both case and control. LSCS is more in control group. Forceps and breech more in case.

TABLE - IX

BIRTH ASPHYXIA

Birth Asphyxia	Cases (n = 200)	Control (n = 200)
Present	63.5% (125)	13.4% (27)
Absent	36.5% (75)	86.6% (173)

Birth Asphyxia is predominant in case.

TABLE - X

MULTIPLE BIRTH

Multiple Birth	Cases (n = 200)	Control (n = 200)
Present	4.6% (9)	6.4% (13)
Absent	95.4% (191)	93.6% (187)

TABLE - XI

MATURITY

	Cases (n = 200)	Control (n = 200)
Preterm-As per History	1% (2)	2% (4)
Preterm-As per History + Record	19.3% (38)	13.9% (22)
Term-As per History	30.5 (60)	39.6 (80)
Term-As per History + Record	50% (100)	46.5 (94)
Post Term-As per History	-	-
Post term-As per History + Record	-	-

Term is more common in both cases and control.

TABLE - XII

BIRTH WEIGHT

Birth Weight	Case (n = 200)	Control (n = 200)
Low Birth Wt as Per History	3% (6)	2% (4)
Low Birth Wt as per History + Record	21.8% (43)	5.9 (12)
Normal birth Wt History	31% (64)	46.5% (90)
Normal birth Wt as per History + Record	44.2% (87)	47.5% (94)

Normal Birth Weight babies are more common in case groups.

TABLE - XIII

HISTORY OF NEONATAL SEIZURES

H/o Neonatal Seizures	Case (n = 200)	Control (n = 200)
Present	70% (140)	-
Absent	30% (60)	100%

Neonatal Seizures is an important risk factor for seizures with Cerebral Palsy.

TABLE XIV

HYPERBILIRUBINEMIA

HYPERBILIRUBINEMIA	Case (n = 200)	Control (n = 200)
Present As per History	4.6% (9)	0% (10
Present As per History + Record	17.3% (34)	2.5%(5)
Absent As per History	32% (63)	49% (99)
Absent As per History + Record	46.2% (91)	48.5% (98)

TABLE - XV

SEIZURES DURING THE 1ST YEAR OF LIFE

	Case (n = 200)	Control (n = 200)
Present	70% (140)	-
Absent	30% (60)	100%

TABLE - XVI

FAMILY HIS TORY OF SEIZURES

	Case (n = 200)	Control (n = 200)
Present	16.7% (35)	20% (42)
Absent	83.3% (165)	80% (158)

TABLE - XVII

TYPE OF CEREBAL PALSY

Type of CP	Case (n = 200)	Control (n = 200)
Spastic Hemiplegic	13.7% (27)	10.9% (21)
Spastic Diplegic	16.2%(33)	29.7% (60)
Spastic quadriplegic	48.7% (97)	6.4% (13)
Dyskinetic	4.6% (9)	6.9% (13)
Mixed	1.5% (3)	17.8% (36)
Hypotonic	15.2% (31)	28.2% (57)

Spastic Quadriplegia is more common in case group.

Spastic diplegia is more common in control group.

TABLE XVIII

SEVERITY OF CP (FUNCTIONAL CLASSIFICATION)

	Case (n = 200)	Control (n = 200)
Able to carryout activity of daily living	14.7% (32)	33.2% (67)
Ambulant with out support	1.5% (3)	11.9% (23)
Ambulant with support	22.8% (45)	37.1% (75)
Bed ridden	60.9% (120)	17.3% (35)

TABLE - XIX

TYPE OF SEIZURES

	Case (n = 200)
GTCS	81.2% (142)
GTS	-
Myoclonic	14.2% (28)
Absence	-
Focal Motor	1% (3)
CPS	2.5% (5)
Status Epilepticus	-
Febrile Seizure	-
Others	10.5% (22)

TABLE - XX

PATTERN OF SEIZURE

	Case (n = 200)
Single	40.1% (79)
Multiple	59.9% (121)

TABLE - XXI

MAXIMUM DURATION OF SEIZURE DURING THE PAST

	Case (n = 200)
<5 mins	46.7% (92)
5-30 mins	18.8% (37)
>30 mins	34.5% (71)

TABLE - XXII

NO. OF FITS ON AN AVERARGE OF ONE YEAR

	Case (n = 200)
Single Episode	36.5% (75)
2-6 Episodes	27.5% (54)
>6 Episodes	36% (71)

TABLE - XXIII

ON MEDICATION

	Case (n = 200)
Monotherapy	39.1% (78)
Polytherapy	58.4% (117)
Not taking treatment	2.5% (5)

TABLE - XXIV

NEURO IMAGING

CT BRAIN

	Case (n = 200)	Control (n = 200)
Cong. Malformations	26.4% (52)	10.4% (19)
Intracranial Haemorrhage	6.6% (13)	1.1% (2)
Periventricular Leucomalacia	18.8% (37)	5.5% (10)
Others	48.2% (95)	83.1% (152)

CT was not taken for 17 children in Control group, 3 children in case

DISCUSSION

There are several studies to find out the risk factors for Seizures in children with Cerebral Palsy.

DEMOGRAPHIC AND FAMILY HISTORY RELATED

Two Fifty Two (63.2%) cases were male in the present study. A similar observation was made by Singhi P, Jagirdar S, Khaudelwal N, Malhi P. et al (73). In their study, 65 out of 105 Cerebral Palsy cases were male. Equal number of boys and girls in the study of A.K. Gururaj et al. (55). Rural or urban resident were included in our study. Rural population contributed to 252 (63.2%), Urban population 148 (268%). Rural population contributed to home delivery and birth asphyxia which is delt later.

Socio Economic States - daily wages contributed to 193 (48.4%) followed by salaried (25.1%) 100. Literacy rate were good but mainly contributed by middle school and above.

Maternal Factors - Like place of delivery, Type of Delivery, Birth Asphyxia, and Multiple Birth.

Place of Delivery - Home delivery which is common in our country, especially when not attended by trained personnel has been identified as an important risk in the present study. Total Number of home delivery 48 (11.3%). In this, case contributed to 18 (7.1%) control 30 (14.9%). This is an area of high priority where all our maternal and child health services are directed towards, and still needs continued vigilance. Institutional Delivery - 352 (88.7%) it included all the high risk pregnancy and the type of deliveries.

Normal vaginal delivery is more in both case & control 59.1% (236). Similar study by Nelson et al (1). Prolonged vaginal 66 (23.4%) with more incidence of birth asphyxia. Prolonged labour is another important risk for CP in the present study. Opinion is divided in the literature about its significance. It was found in 42 (21%) cases in the study as against 18 out of 544 (3.3%) cases in Srivastava's series (23). Nelson & Ellenberg state in their study (4) that contrary to their expectations, prolonged labour was not significant predictor. So also, the two national cohort studies of the United Kingdom (15) which is also a case control study, found a lack of association with prolonged duration of labour and the authors explain that birth asphyxia may be due to a pre-existing problem and not due to intrapartum adversities.

Caesarian sections 93 cases, control (59) 30.2%, In cases 34 (17.3%) Caesarian section are associated with high risk pregnancies, there should be expert management & timely intervention to prevent Cerebral Palsy. Instrumental delivery by forceps or vacuum extraction constitutes a risk in the present study with forceps 19 (4.8%) with increase in cases to 13 (6.6%) with birth asphyxia. A similar picture is seen in the case control study by Sahu Suvanand where instrumental assisted delivery is a significant risk. Torfs et al did not find instrumental assisted delivery as a significant risk. (20).

Although breech presentation was present only in 3 cases out of 200 it was also significant risk for seizure. In Srivastava's series, 21 out of 544 cases had breech presentation. Breech delivery was not a significant risk factor in the study by Sahu Suvanand (2.4% of cases). Western studies like the NCPP identified breech presentation, but not breech delivery as an important risk. In the NCPP study, 11.1% of cases had breech presentation. Nearly one third of the CP cases who had breech presentation had an associated congenital malformation. It was

postulated that it may be the result of an underlying developmental abnormality of the fetus.

Birth Asphyxia

In the Present study birth asphyxia seen in 152 (38.3%) of Study population. (63.5% Vs 36.5%) and absent (36.5% Vs 86.6%) case and control respectively. In cases (Cerebral Palsy with Seizures) asphyxia was more contributing to 63.5% against 36.5% which is also high. Forty out of 189 (211%) children with cerebral palsy had asphyxia in the NCPP study (4). The same study has observed that in the immediate postpartum period, delay in the first cry was and important predictor. Still, the authors consider both birth asphyxia and Cerebral Palsy to be the effect of a single underlying factor instead of asphyxia being the cause of Cerebral congenital anomalies or other factors present before the onset of labour that might have increased their vulnerability to intrapartum events. Blair et al in their western Australian study (5) found a significant association between intrapartum asphyxia and Cerebral Palsy. But, they too consider asphyxia to be the effect of prenatal problem rather than a cause of CP because in their study only 15 out of 189 (8%) CP cases were found to have intrapartum asphyxia. Naeye et al (24) found that birth asphyxia had the highest relative risk for quadriplegic CP though the frequency of birth asphyxia in the population was very low and was seen in only 9 out of 150 (6%) cases. Torfs et al (20) found 9 out of 41 (22%) CP cases to have birth asphyxia with significant association between the two. All but one had one or more compromising maternal or gestational factors or a major congenital defect. Nelson and Ellenberg in their study on Apgar scores as predictor of major neurological disability (26) found that low Apgar scores were significant risk factors for cerebral palsy, though 80% of them were free of any handicap. Misra et al (29) made similar observation like Nelson and Ellenberg that neurodevelopmental

outcome correlated inversely with the Apgar scores at 5 and 10 minutes. Hagberg and Hagberg (11) (Swedish studies) have found significant association between perinatal causes and CP and the trend in the incidence of CP over 20 years period correlated with that in perinatal factors. Intrapartum anoxia was found in 133 out of 544 (24.5) cases of Srivastava's series (23). In Sahu Suvanand's study birth asphyxia was present in 26% of cases and it was the second most common risk factor for CP with odds ratio of 36.1 next to low birth weight.

Multiple Birth

There was total number of 22 multiple birth in both case and control. 9 out of 22 in the study group (case) contributed more to preterm, low birth weight, birth asphyxia and congenital malformation.

Neonatal Factors - Maturity & Birth Weight

Low birth weight has been consistently and uniformly appreciated as an important risk and this is well reflected in the present study. 62 (24.8%) cases were low birth weight babies. Nelson & Ellenberg identified low birth weight as the single most important predictor in the immediate post partum period. The Swedish study (11) has also identified a consistent and good correlation between the two. Thirty seven percent of CP children in the Swedish study were low birth weight babies and is similar to the observation in the present study. Torfs et al (20 found a six fold higher risk of CP for LBW babies, LBW forming 17% of CP cases with the OR of 2.8, 95% CI 0.8 - 6.3. Paroah et al (16) identified a significant increase in prevalence of CP among LBW infants. Apart from this, a trend of increasing risk for CP with decreasing birth weight was also identified by the above studies. This is well brought out in the study of

Murphy et al (31) who found a significant increase in risk of CP with decreasing birth weight was also identified by the above studies. This is well brought out in the study of Murphy et al (31) who found a significant increase in risk of CP with decreasing birth weight p value for the trend being < 0.03. This is also reflected by the NCPP study of Nelson and Ellenberg (4) the risk of CP increasing from 3.4 per 1000 when the birth weight is > = 2500 g to 13.9 per 100 among 1500 to 2500 g and to as high as 90.4 per 1000 in those with VLBW (< = 1500 g). The national cohort study of the United Kindgom (15) found the prevalence of CP to increase from 1.6 per 1000 among babies who weighed > 2500 g at birth to 14.4 per 1000 in the LBW babies. In the Californian study by Cummins (36). 48% of CP cases had birth weight < 2500 g and 28% being < 1500 g. LBW was the single most important risk factor associated with CP in the case control study by Sahu Suvanand OR 13.3 (95% CI 4.95 - 38.2) (30). In the present study, in 63 (31.5%) cases birth weight was not known as against only 6 (3%) controls. The increased association of maternal illiteracy with CP may be reflection of this. Among the cases for whom birth weight was known, 64 (46.7%) were LBW babies, of whom 8 (5.83%) were < 1500 g, 17 (12.4%) 1500-200 g and 73 (28.5%) 2001 g to 2499 g.

The present study shows that of the children with CP whose birth weight was known, belonged to the LBW category. This underlines the importance of the need for rigorous antenatal services and control of adverse antenatal factors identified to result in low birth weight infants. Kulak W, Sobaniec W. (67). Zelnik N, et al (70). Hadjipanayis A, et al (71), Kulak W, et al (67), Singhi P, et al (73) in all this above studies generalized tonic clonic seizures with multiple episodes lasting more than 5 minutes requiring polytheraphy or

common.

Classification of the type of epilepsy is often difficult in children with CP for many reasons; firstly the partial onset prior to generalization may not be apparent or witnessed; impairment of consciousness during ictal period may be difficult to detect in a child with severe handicaps; lastly the differentiation between myoclonic, brief tonic and atonic seizures could be difficult without ictal EEG or video EEG.

The increased risk of epilepsy in CP is believed to be linked to genetic and perinatal factors. First-degree relatives of children with CP and seizures have been reported to have an increased incidence of seizures. Among the perinatal factors, structural and developmental defects of the brain, chromosomal defects, intrauterine infections and hypoxic ischemic brain injuries are the more obvious causes that may result in seizures.

Zelnik N, et al (70), Sugiura C, et al (68) Presence of at least one abnormal structural finding (particularly brain atrophy) was also a significant predictor of epilepsy. CT findings in the presents study, 26.4% has more congenital malformations in the form of following. Significant brain volume reduction, periventricular leucomalacia, basal ganglia changes, multicystic encephalopathy and schizencephaly, Focal abnormalities such as infarction, focal atrophy, cerebellar atrophy, and mesial temporal sclerosis were the major abnormalities seen. Significant brain volume reduction and schizencephaly are the radiological sign that were more common in case. Basal ganglia changes were present in control group. It is difficult to explain why the children in control group did not have seizures in spite of significant radiological abnormalities.

A.K. Gururaj, et al (55) half of the study group presented with generalizded tonic clonic seizures, the EEG showed focal epileptic discharges with or without secondary generalization 39.3%. Singhi P, et al (73) EEG abnormalities were seen in 70.5%. In the present study group only 163 EEG were taken all of which showed abnormalities.

The objective of the study was to explore the relationship between cerebral palsy and epilepsy. Epilepsy is more common in certain types of CP than others with tetraplegic variety having the highest incidence of seizures (15 to 16%) which in turn, might be a reflection of the severity of damage to the brain. In the current study spastic tetraplegia was the commonest type of CP complicated by seizures. Spastic diplegia was the commonest type of CP in the control group of CP without seizures. Generalized tonic clonic type of seizures was more common. Epilepsy was found to have an earlier age of onset, poorer seizure control, increased risks of status epilepticus and a need for more than one antiepileptic drug for seizure control in children withCP and seizures. There was also a higher incidence of neonatal seizures in this group of children as compared with control group. This possibly reflects a more severe birth asphyxia. In particular, children with spastic tetraplegia more often needed polytherapy. This may be due to the more extensive brain pathology seen on brain imaging in this group of children. It is also possible that certain genetic factors, as yet unidentified, may play a role in the pathogenesis of seizures in children with CP, particularly in the tetraplegic variety. When we compare the two groups of children with CP with seizures and those without seizures. The following variables seem to have an increased association with the seizures group: history of birth asphyxia, term delivery, a history of neonatoal seizures, spastic tetraplegic variety of CP, history of seizures in first year of life, type of seizures and presence of abnormal CT findings.

CONCLUSIONS

1. Risk factor for Seizures in children with cerebral palsy were rural population, low socio economic status, home delivery, low birth weight, preterm, birth asphyxia and multiple births.

2. All the risk factors which are identified to be significant are preventable by an efficient health care delivery system and good health education strategies. These are the area of high priority.

3. Health education to reduce early marriage and pregnancy and to avoid home delivery will help to eliminate the risk factors. Good antenatal care will reduce the incidence of low birth weight. Improvement of obstetric care and effective management of prolonged labour and difficult labour will also help to reduce the problem of birth asphyxia and complications of multiple births.

4. Congenital malformation of Central Nervous System by CT brain/MRI are being commonly, identified in both the case and control in the present study (26.4%, 10.4%) respectively. Periventricular leucomalacia is more in spastic diplegia.

5. Seizures are more common in certain types of cerebral palsy than other with Spastic quadriplegia variety having the highest incidence of seizures raging from 40-60% which in turn might be a reflection of the severity of damage of the brain. Spastic quadriplegia being the most common type in this study with spastic diplegia in the control.

6. Generalized tonic clonic seizures, multiple episodes, lasting more than 5 - 30 minutes with more than 2-6 episodes per year, requiring polytherapy is found to be common in this study.

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Institute of Child Health and Hospital for Children

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Date: 9.6.2008

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Institute of Child Health and Govt.
Hospital for Children, Chennai 8.
Dated: -06-08

The Institutional Review Board (Ethical Committee) of Institute of Child Health and Hospital for Children, Chennai was held on 13.5.2008 at 2.00 PM at the Deputy Superintendent's chamber.

MEMBERS PRESENT: Dr.R.Kulanthai Kasthuri,
Chairperson

Members:

1. Dr.K.Gita
2. Dr.P.Jeyachandran
3. Dr.T.Jothi
4. Dr.Paramanantham
5. Dr.D.Vijayasekaran
6. Prof.Girija Shyam Sundar
7. Mrs.Muthulakshmi, Advocate
8. Dr.P.Ramachandran

Title: **"Risk Factors for Seizures in Children with Cerebral Palsy".**

The Institutional Review Board was satisfied with the revised format submitted by you. Hence the Institutional Review Board is pleased to approve the study.

Institute of Child Health and Hospital - 9 JUN 2008 Egmore, Chennai-600008

9/6/08
Director and Superintendent

Director and Superintendent
Institute of Child Health and
Hospital for Children
Egmore, Chennai - 600 008.

To
Dr.B.Rajesh Kannan
Post Graduate
Institute of Child Health and Hospital for
Children,
Chennai 600 008